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Association of Hydrotropes in Aqueous Solution Studied by Reaction Kinetics

Niklaas J. Buurma,[a] Michael J. Blandamer,[b] Jan B. F. N. Engberts[a]*

[a] Physical Organic Chemistry Unit, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
Fax: (+31)-50-363-4296, e-mail: J.B.F.N.Engberts@chem.rug.nl
[b] Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK
E-mail: MJB@le.ac.uk

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Abstract: The effect of added hydrotropes on the rates of neutral hydrolysis for 1-benzoyl-3-phenyl-1,2,4-triazole **1** has been studied, together with the concentration dependence of the ^{1}H NMR spectra of the hydrotropes in aqueous solution. Hydrotropes include sodium 4-alkylbenzenesulfonates **2a – e**, sodium 4-methoxybenzenesulfonate **2f**, sodium 4-hydroxybenzenesulfonate **2g**, cesium benzenesulfonate **3**, benzamidinium chloride **4**, phenyltrimethylammonium bromide **5a**, and benzyltrimethylammonium bromide **5b**. All hydrotropes, except **2g**, induce strong rate-retarding effects, indicative of strong interactions with **1** and of remarkably strong hydrophobic interactions between aromatic moieties. Most hydrotropes show neither spectroscopic nor kinetic evidence for cooperative aggregation in the concentration range studied, i.e., from 0 to 1.4 mol kg^{-1}. Cooperative aggregation is absent because the hydrophobic moieties are too small for hydrophobic interactions to overcome electrostatic repulsion. Lack of aggregation results in high availability of hydrophobic binding sites, thereby accounting for the high solubilizing power characteristic for hydrotropes. However, sodium 4-*n*-propylbenzenesulfonate **2d** and sodium 4-*n*-butylbenzenesulfonate **2e** show cooperative self-association forming highly dynamic loose micellar-type structures.

Keywords: encounter complexes; hydrolyses; hydrophobic interactions; hydrotropes; kinetics; water as solvent

Introduction

Water is an interesting and useful solvent in organic chemistry.[1–4] Unfortunately, the ability of liquid water to drive apolar molecules together is often seen as a disadvantage. However, it is precisely this property that can be used with advantage for bimolecular (catalytic) reactions, as the coming together of reactants and/or catalysts is a prerequisite for those processes. Further, solvent water may also act as a catalyst by, for example, hydrogen-bond stabilization of an activated complex.[5]

Reactant-catalyst interaction is an important topic in current research. Further insight into such interactions should lead to an improved rational design of catalysts for use in aqueous solutions. To gain a better understanding of such interactions, we have studied the effect of cosolutes on a variety of chemical reactions in aqueous solution.[6,7] The cosolutes fall in three groups; (i) hydrophilic or weakly hydrophobic cosolutes, (ii) hydrotropes, and (iii) surfactants, the latter being able to form a range of aggregate structures, largely depending on their molecular shape.

In the present study, we used hydrotropes as cosolutes. Hydrotropes normally comprise hydrophilic and hydrophobic moieties, with the hydrophobic moiety being typically too small to induce micelle formation. Hydrotropes induce a characteristic steep increase in aqueous solubilities of hydrophobic compounds around a certain characteristic concentration, after which the solubilities often remain unchanged.[8] For organic synthesis in aqueous solutions, the use of hydrotropes can be beneficial, for example, in the microwave-enhanced Hantzsch dihydropyridine ester synthesis,[9] and the Claisen–Schmidt reaction[10] in aqueous solution. In addition, hydrotropes enhance rates of reaction in multiphase transformations.[11]

In order to probe non-covalent interactions between hydrophobic solutes, we have studied the effects of sodium 4-alkylbenzenesulfonates **2a – e**, sodium 4-methoxybenzenesulfonate **2f**, sodium 4-hydroxybenzenesulfonate **2g**, cesium 4-methylbenzenesulfonate **3**, benzamidinium chloride **4**, and aromatic ammonium bromides **5a**, **b** (Scheme 1) on the water-catalyzed hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole **1**. These hydrotropes are not sufficiently basic to act as general bases in

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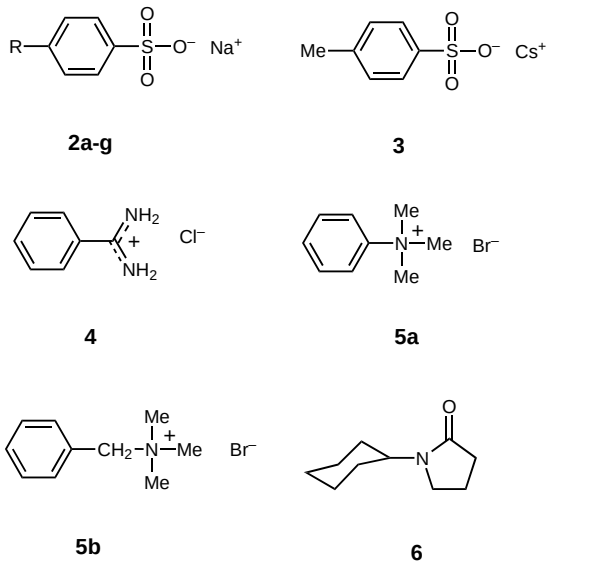
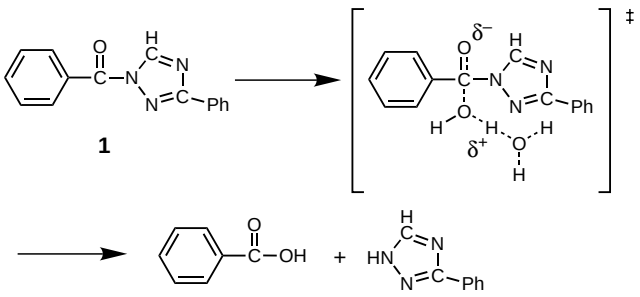


Scheme 1. Hydrotropes **2a** (R = H), **2b** (R = Me), **2c** (R = Et), **2d** (R = *n*-Pr), **2e** (R = *n*-Bu), **2f** (R = MeO), **2g** (R = HO), **3**, **4**, **5a**, and **5b** used in the present study.

the hydrolysis of **1** (*vide infra*). Furthermore, we determined the concentration dependence of the ^{1}H NMR spectra of benzenesulfonates **2b**, **d**, and **e** in D_2O in order to study the self-association of the hydrotropic cosolutes in a probe-independent way.

The pH-independent hydrolysis of **1** proceeds via the mechanism shown in Scheme 2.[12,13] The reaction is water-catalyzed between pH 3 and 5. The reaction proceeds via a dipolar activated complex in which two water molecules, one acting as a general base, are involved with three protons in flight.

Computer simulations of a closely related hydrolysis reaction, using both quantum and classical dynamics, reveal that significant proton tunnelling is involved in the rate-determining step.[14] Consequently, water molecules involved in the activated complex are subject to severe orientational constraints. Consistent with this mechanism, standard entropies of activation are strongly negative.[12]



Scheme 2. Mechanism of the pH-independent hydrolysis of 1-benzoyl-3-phenyl-1,2,4-triazole **1**.

Hydrolysis of these activated amides[6] and related activated esters,[13] is retarded by sufficiently hydrophobic cosolutes.[6] A semi-thermodynamic theory describing interactions between a reacting molecule and an inert hydrophobic cosolute was developed several years ago.[15,16] Rate retardations reflect the effect of added cosolute on the activity coefficients of initial and transition states of the substrate undergoing hydrolysis. These coefficients are re-expressed using the procedures described by Wood[17] in terms of pairwise solute-solute interaction parameters. The analysis leads to Equation (1).

$$\ln\left[\frac{k(m_c)}{k(m_c=0)}\right]=\frac{2}{R\cdot T\cdot m_o^2}\cdot\left[g_{cx}-g_{c\neq}\right]\cdot m_c-N\cdot\phi\cdot M_l\cdot m_c \qquad (1)$$

Here $k(m_c)$ is the (pseudo-)first-order rate constant for hydrolysis in an aqueous solution molality m_c of cosolute c; $k(m_c = 0)$ is the rate constant in the absence of added cosolute, R the gas constant and T the temperature. Significantly, $[g_{cx}-g_{c\neq}]$ is the difference in interaction Gibbs energies between the cosolute c and the reactants x on one hand and the cosolute c and the activated complex $\neq$ on the other hand. M_l is the molar mass of water, N is the number of water molecules involved in the rate-determining step, and ϕ is the practical osmotic coefficient for the aqueous solution where the molality of added solute is m_c. In the present study, N equals 2 (*vide supra*). Since the solutions are very dilute, ϕ can be taken as unity; m_o, 1 mol kg^{-1}, is the molality of the solute reference state. The quantity $[g_{cx}-g_{c\neq}]$ is denoted as G(c). Kinetic data for a wide range of reactions have been analyzed in this manner.[6]

The rate-retarding effect produced by hydrophobic cosolutes is primarily an initial state effect,[18,19] G(c) therefore describes stabilization of the initial state. Stabilization of the initial state of the reaction can be understood in terms of the formation of a substrate-cosolute encounter complex.[20] Hydrolysis is inhibited in these encounter complexes, leading to the rate equation given in Equation (2).[20]

$$k(m_c)=\frac{k(m_c=0)}{1+K_{ec}\cdot m_c} \qquad (2)$$

Here $k(m_c)$, $k(m_c = 0)$ and m_c are defined as for Equation (1), K_{ec} is the equilibrium constant of encounter complex formation. These encounter complexes are stabilized by hydrophobic interactions.[20] Equations (1) and (2) are related via the Taylor expansion of Equation (2), giving Equation (3).

$$\ln\left\{\frac{k(m_c)}{k(m_c=0)}\right\}=-\ln\left\{1+K_{ec}\cdot m_c\right\}\approx -K_{ec}\cdot m_c \qquad (3)$$

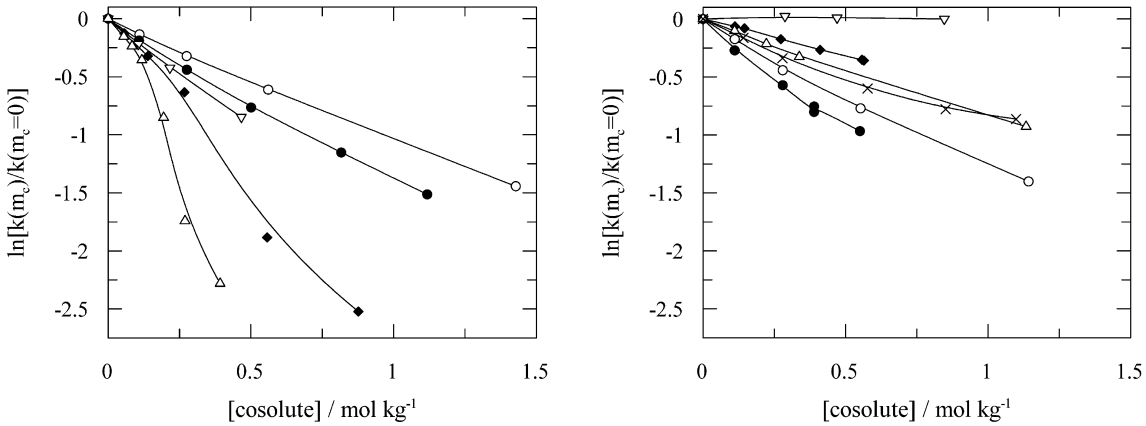


Figure 1. The effect of different hydrotropes on the hydrolysis of **1**. *Left*: the alkylated benzenesulfonates **2a** (○), **2b** (●), **2c** (▽), **2d** (◆), **2e** (△). *Right:* **2f** (●), **2g** (▽), **3** (○), **4** (×), **5a** (◆), and **5b** (△).

As follows from comparison of Equation (3) with Equation (1), a lower (more negative) G(c) corresponds to a more stable encounter complex.

Results and Discussion

All tested hydrotropes, except **2g**, induce strong rate retardations (Figure 1). The hydrotropes bearing longer alkyl chains, **2d** and **2e**, show sigmoidal dependence of $\ln[k(m_c)/k(m_c=0)]$ on molality of added cosolute, indicative of cooperative self-association.

Kinetics of Reactions in Dilute Solutions of Hydrotropes

For all hydrotropes, plots of $\ln[k(m_c)/k(m_c=0)]$ against molality of hydrotrope [see Equation (1)] were constructed for the concentration range up to 0.3 mol kg^{-1} (0.1 mol kg^{-1} for **2e**). This molality range has been chosen in order to avoid possible complexities in the data due to 2:1 and higher order interactions. All plots show a linear dependence of $\ln[k(m_c)/k(m_c=0)]$ on molality of hydrotrope (Figure 2). This pattern accords with the results of Friberg et al.[21] who showed that the vapor pressure of phenylethyl alcohol decreases linearly with the concentration of added sodium xylenesulfonate up to concentrations of the latter to at least 0.5 mol % (0.25 mol kg^{-1}). The slopes of the plots of $\ln[k(m_c)/k(m_c=0)]$ vs. m_c for the dilute region yield the G(c)-values given in Table 1.

All G(c)-values are large and negative (apart from that for **2g**), indicating strong inhibition of hydrolysis by substrate-solute interactions involving added hydrotropes. In terms of the model leading to Equation (2), the observed pattern is consistent with the formation of relatively stable encounter complexes with equilibrium constants of formation K_{ec} all larger than unity, except in the cases of **5a** and **5b**. The values for K_{ec} are comparable to those found by Ueda.[22] Encounter complexes between **1** and **5a** and **5b** are unstable ($\Delta G_{ec} > 0$) with

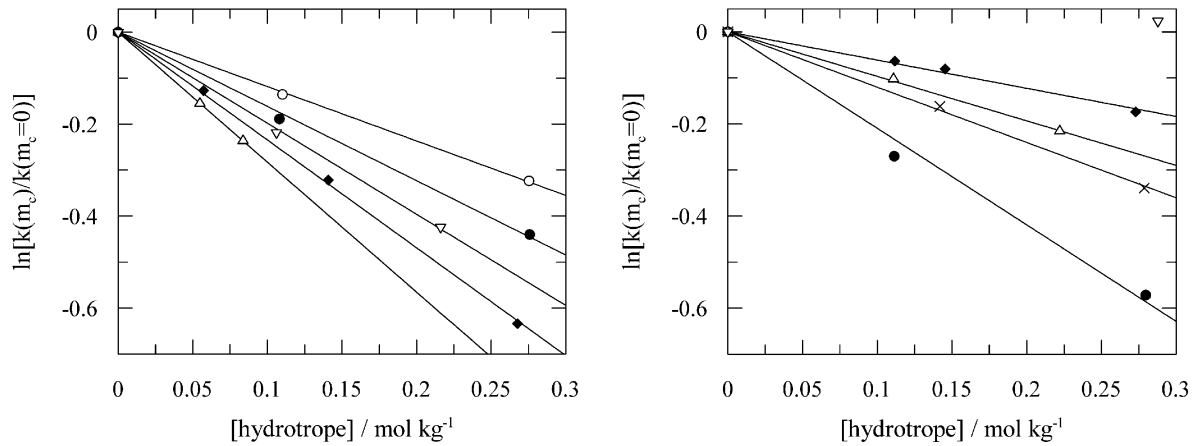


Figure 2. The effect of different hydrotropes on the hydrolysis of **1** at low concentration. *Left*: the alkylated benzenesulfonates **2a** (○), **2b** (●), **2c** (▽), **2d** (◆), **2e** (△). *Right:* **2f** (●), **2g** (▽), **3** (○), **4** (×), **5a** (◆), and **5b** (△).

Table 1. G(c) values of hydrotropes **2a – g**, **3**, **4**, and **5a**, **b** at 298 K.

Hydrotrope	G(c) [J kg mol^{-2}]
2a	-1475 ± 25
2b	-1950 ± 50
2c	-2408 ± 37
2d	-2858 ± 30
2e	-3456 ± 6
2f	-2551 ± 116
2g	~ 0
3	-1909 ± 6
4	-1443 ± 27
5a	-715 ± 26
5b	-1153 ± 8

respect to the individually solvated molecules. Previously, significantly negative G(c)-values were also reported for the effects of added aromatic α-amino acids on the rate constants for hydrolysis of **1**.[23] In combination with the present results, this suggests that hydrophobic interactions involving aromatic molecules are particularly strong.

Thermodynamics of solution of aromatic molecules in aqueous solutions are different from that of aliphatic molecules in that standard Gibbs energies of transfer from the gas to the aqueous phase are negative for aromatic molecules, whereas they are positive for aliphatic molecules. This was shown to be mainly an enthalpic effect, attributed to the aromatic ring being able to accept hydrogen bonds from hydration-shell water molecules.[24,25] It was also concluded that the interactions between aromatic molecules are more favorable than those between comparable aliphatic molecules.[24]

For **2a – e**, G(c) varies linearly with the number of methylene groups in the alkyl chain (Figure 3), in accord with the Savage–Wood Additivity of Group interactions (SWAG) theory.[17] The decrease in G(c) per methylene unit, viz. -500 ± 131 J kg mol^{-2}, is large in comparison with previously reported estimates. Typically, increment values for undisturbed methylene units are in the order of -100 J kg mol^{-2},[26,7] although values up to -340 J kg mol^{-2} have been observed for the less hydrophobic substrate 1-benzoyl-1,2,4-triazole.[27]

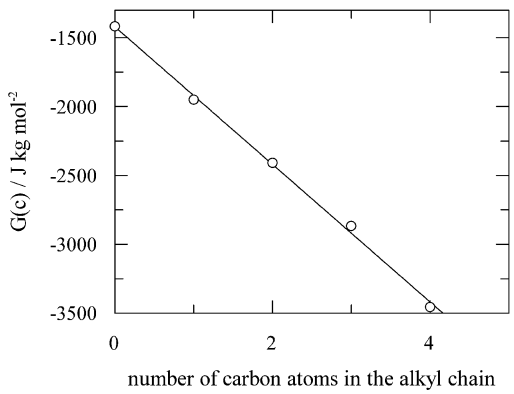


Figure 3. G(c) as a function of the number of methylene units in the alkyl-chain of **2a – e**.

The remarkably high group contribution of the methylene group to the present G(c)-values is attributed to a synergistic effect of the aromatic benzenesulfonate moiety and of the methylene groups. Sodium benzenesulfonate itself is a potent inhibitor of the reaction, as can be seen from the G(c) of **2a**. In terms of the analysis leading to Equation (2), the observed low G(c) corresponds to a rather stable encounter complex which inhibits the reaction.[20] Further hydrophobic stabilization of this encounter complex by elongating the alkyl chains of the added hydrotropes increases the rate-retarding effect.

Surprisingly, the rather polar **2f** induces a rather strong rate retardation, comparable to that of **2c**. Previously, shielding of hydrophobicity by hydrophilic groups has been attributed to the prevention of the formation of a hydrophobic hydration shell.[6] We contend that the methyl and phenyl moieties prevent formation of a hydrophilic hydration shell around the oxygen, resulting in the oxygen's hydration shell becoming part of a slightly disturbed hydrophobic hydration shell of its neighboring groups. Hence the oxygen is masked as a hydrophilic moiety in 1:1 hydrophobic interactions.

For the hydroxy-substituted benzenesulfonate **2g**, G(c) is positive but small. General-base catalysis by the deprotonated phenol is expected to be negligible as the pK_a of **2g** was determined to be 8.6 by titration of a 0.5 mol % solution. Lack of hydrophobic interaction between **2g** and **1** occurs as an exact opposite of the behavior of **2f**. Here, the hydrophobic nature of the phenyl ring is masked by the hydration shells of the hydrophilic sulfonate and hydroxy group, making the phenyl ring unavailable for hydrophobic interactions. Similar behavior has been found for L-proline, where 4-hydroxylation results in a total loss of hydrotropic behavior.[28] It is clear from the mole fraction solubilities of phenol and methoxybenzene, being 1.78×10^{-2} and 1.75×10^{-3}, respectively,[29] that the phenolic compound is far more hydrophilic than the methoxy-substituted benzene.

In order to investigate the effect of the relative electron density in the aromatic ring, non-alkylated hydrotropes **2a**, **4**, **5a**, and **5b** were studied. Aromatic interactions are strongest for donor-acceptor systems, followed by acceptor-acceptor systems whereas electron-rich aromatic species do not stack well because the aromatic π-clouds repel each other.[30] Kinetically, at low concentration, the non-alkylated cationic hydrotrope **4** strongly resembles the non-alkylated anionic hydrotrope **2a**. The average chemical shifts of the aromatic

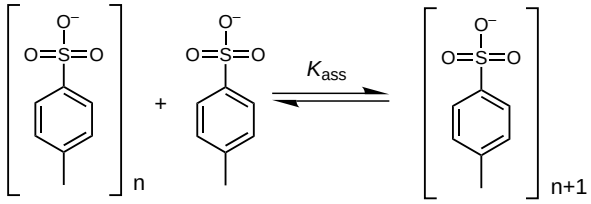
Table 2. ^{1}H NMR chemical shifts of aromatic protons of hydrotropes **2a – g**, **3**, **4**, and **5a**, **b**.

Hydrotrope	δ [ppm] Average
2a	7.68
2b	7.52
2c	7.55
2d	7.54
2e	7.55
2f	7.41
2g	nd
3	nd
4	7.68
5a	7.72
5b	7.55

nd: not determined.

protons show that the electron density in the aryl rings of **2a** and **4** is similar (Table 2). Based on the higher average NMR chemical shift, the aromatic ring of the non-alkylated cationic hydrotrope **5a** is more electron-deficient than that of **2a** and **4**. Considering that both aromatic rings in **1** are relatively electron-deficient, **5a** is expected to interact more weakly with **1**, leading to a less negative G(c) value, as borne out in practice. Structurally related **5b**, having a lower average chemical shift, is intermediate in G(c). Even though G(c) shows no correlation with the average chemical shift of the aromatic protons, the lack of correlation with average chemical shifts alone is caused by the fact that the trimethylammonium moiety of **5b** is not directly attached to the aromatic ring. The hydrophilic hydration shell around the ionic moiety will therefore not overlap as strongly with the hydration shell of the aromatic ring as is the case for **2a**, **5a**, and **4**. Consequently, the hydrophobicity of the aromatic ring is less attenuated for **5b**, causing its G(c)-value to be higher than expected on the basis of electron density in the aromatic ring alone, which is indeed observed.

As noted above, the dilute concentration range in which the G(c)-values have been determined was chosen to avoid 2:1 and higher order interactions. To check the validity of this assumption, the concentration dependence of the ^{1}H NMR spectrum of **2b** was examined. The short-chain benzenesulfonate **2b** shows an almost linear dependence of the chemical shift of the *meta* proton on concentration in aqueous solution indicating the absence of cooperative aggregation. The decrease in chemical shift of the *meta* proton is caused by the decrease in interhydrotrope distances upon increasing cosolute concentrations and the accompanying weak, non-cooperative binding between the individual hydrotrope molecules. As a result of the increasing concentration, both intermolecular aromatic ring current effects[31] and the decreasing polarity of the solution[32] will cause an upfield shift.



Scheme 3. Non-cooperative self-association of hydrotropes.

In addition, aggregation into loose micellar-type aggregates would have been associated with a difference in G(c) between **2b** and **3**. Larger aggregates will bind counterions as a result of the increasing charge density with increasing aggregation number. Replacing sodium counterions by cesium counterions is known to have a beneficial effect on association: a less unfavorable dehydration of the cesium cations leads to more efficient stabilization of the double (or higher) positive charge in the dimer (or higher aggregates). In the dilute solutions for which G(c) have been determined, this is not observed.

The equilibrium constants for hydrotrope self-association also suggest the prevalence of 1:1 interactions. The equilibrium constant for encounter complex formation[20] between **1** and any of the investigated hydrotropes does not exceed 3 kg mol^{-1}. We therefore contend that the equilibrium constant of association between individual hydrotropic molecules does not exceed 1 kg mol^{-1} for the investigated systems, since binding between the hydrolytic probe and hydrotropic cosolute is only governed by favorable hydrophobic interactions, whereas binding between two hydrotropic cosolute molecules is counteracted by electrostatic interactions. We assume the equilibrium constants for formation (K_{ass}) of the (n + 1)-mer from the n-mer to be less than 1 kg mol^{-1}, assuming non-cooperative associ-

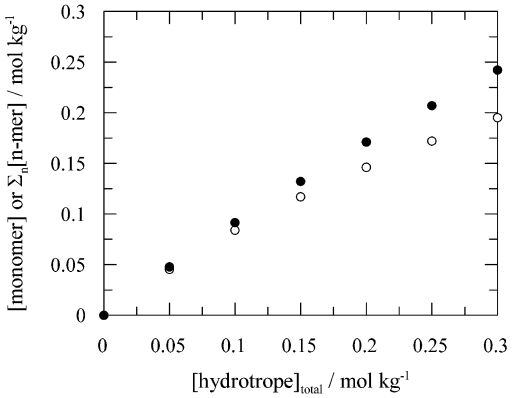


Figure 4. Concentrations of monomers (○) and of oligomers (●) as a function of the concentration of a weakly self-associating solute.

ation (Scheme 3). Using an upper value of 1 kg mol^{-1} for K_{ass}, we calculated the compositions, in terms of monomer and oligomer concentrations,[33] of solutions in which the total hydrotrope concentration ranges between 0 and 0.3 mol kg^{-1} (Figure 4). At all total hydrotrope concentrations ([hydrotrope]$_{total}$), the concentration of monomeric hydrotropic cosolute ([monomer]) is smaller than the total concentration of hydrotropic cosolute. However, the total concentrations of monomers and oligomers combined, Σ_n[n-mer] is only about 20% less than the total hydrotrope concentration and it varies almost linearly with total hydrotrope concentration. Therefore, 1:1 interactions still prevail. For the expected values of K_{ass} smaller than 1 kg mol^{-1}, 1:1 interactions will be the main contribution to G(c).

Kinetics of Reactions in Moderately Concentrated Solutions of Hydrotropes

In the higher concentration range from 0.3 mol kg^{-1} up to 1.5 mol kg^{-1}, kinetic data for hydrolysis in the presence of **2d** and **2e** reveal cooperative self-association of the hydrotropes as indicated by the non-linearity in the plots of $\ln[k(m_c)/k(m_c=0)]$ vs. m_c. This pattern is not observed for the shorter-chain benzenesulfonates **2a – c** and the other hydrotropes. For example, in the case of sodium 4-methylbenzenesulfonate, an archetypal hydrotrope, $\ln[k(m_c)/k(m_c=0)]$ is linearly dependent on hydrotrope molality, the deviation being towards higher values of $\ln[k(m_c)/k(m_c=0)]$ at higher molalities. This pattern is generally observed for non-associating cosolutes. The deviation at higher concentrations is attributed to non-cooperative self-aggregation. For the non-alkylated hydrotropes, this trend is strongest for **4** (Figure 5), indicating that the cationic charge is most effectively dispersed in the aromatic moiety of **4**, thereby reducing the electrostatic repulsion between the monomers. The other non-alkylated hydrotropes show linear plots of $\ln[k(m_c)/k(m_c=0)]$ versus molality,

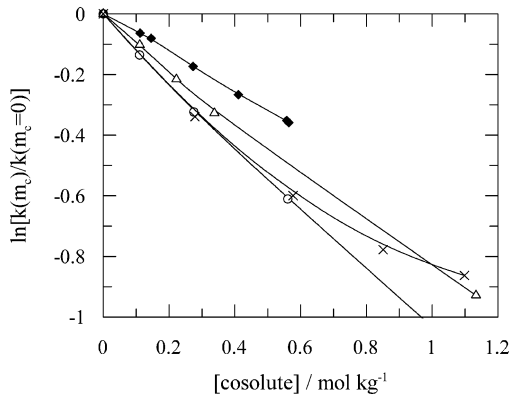


Figure 5. The effect of different non-alkylated hydrotropes on the hydrolysis of **1**; **2a** (○), **4** (×), **5a** (◆), and **5b** (△).

indicating that the properties of the solutions are controlled by pairwise solute-solute interactions even at fairly high concentrations. This result not only excludes the possibility of cooperative self-association in this molality range, it also indicates that K_{ass} (for non-cooperative association between the hydrotropes) is small, most probably significantly smaller than 1 kg mol^{-1}. The low value of K_{ass} results from the charge repulsion in competition with hydrophobic interactions between the hydrophobic moieties. As is clear from the linearity of plots of $\ln[k(m_c)/k(m_c=0)]$ vs. molality, high concentrations of hydrotropes are achievable in aqueous solution, without significant association or phase separation. The fact that $K_{ec} > K_{ass}$ corroborates the conclusion that interactions with uncharged molecules are not hindered by charge repulsion and that interaction between apolar non-ionic solubilizates and ionic hydrotropes is much stronger than interactions between hydrotropic molecules. Consequently, if the hydrophobic moiety of the hydrotrope is made less hydrophobic, for example by introduction of a hydroxy-substituent, a strong decrease in hydrotropic activity is observed.[28]

The lack of strong self-association results in the presence of many "single hydrophobic binding sites", facilitating the dissolution of apolar molecules. Therefore, solubilizing effects of hydrotropes are normally larger than those of surfactants. We also note that these single hydrophobic binding sites can participate in rather strong hydrophobic interactions with apolar solutes, making hydrotropes different from typical salting-in solutes.

The transition from weak association to cooperative association is apparent from a marked change in the molality dependence of $\ln[k(m_c)/k(m_c=0)]$. Weak association is accompanied by higher values of $\ln[k(m_c)/k(m_c=0)]$ than expected on the basis of linear behavior at higher cosolute molalities. Cooperative association, however, is accompanied by sigmoidal plots of $\ln[k(m_c)/k(m_c=0)]$ against molality. First, the slope of plots of $\ln[k(m_c)/k(m_c=0)]$ vs. m_c becomes more negative, a pattern attributed to stronger cooperative binding of **1** to small self-associated clusters of added cosolute molecules. A leveling off at higher molalities occurs as a result of the substrate being almost completely bound. For **2d** and **2e**, the hydrophobic moieties are large enough for hydrophobic interactions to overcome the electrostatic repulsion. As a consequence, small and weakly organized clusters are formed. For both hydrotropic molecules and hydrolytic probe, it now becomes possible to interact favorably with more than one hydrophobic moiety and cooperative binding starts to take place.

In accord with the kinetic data, **2d** and **2e** show a sigmoidal dependence of the chemical shift of the *meta* protons as a function of the concentration (Figure 6), revealing a critical concentration of association. The observed critical hydrophobic interaction concentra-

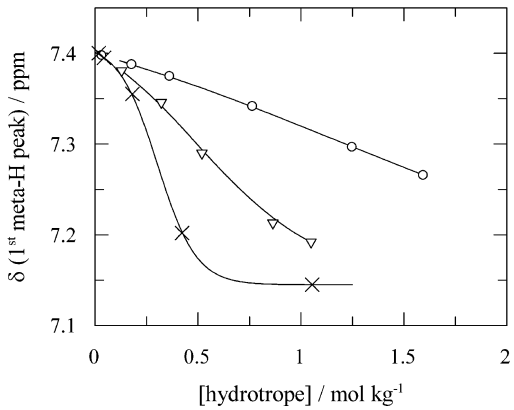


Figure 6. Chemical shift of the meta protons in the aromatic ring of **2b** (○, +0.03 ppm), **2d** (▽) and **2e** (×). Concentrations were calculated after correction for the density difference between H_2O and D_2O.

tions (CHICs) are 0.5 molal and 0.25 molal for **2d** and **2e**, respectively, in accord with the concentrations obtained from the kinetic experiments. Therefore, we contend that in the cases of **2d** and **2e**, the hydrophobic interaction between the non-polar moieties of the molecules is able to overcome the charge-repulsion of the ionic moieties. As a result of this, weakly structured aggregates will be formed cooperatively. In fact, **2d** and **2e** are the link between hydrotropes and surfactants.

In addition to ionic hydrotropes, a few nonionic hydrotropes have been examined previously.[34] As nonionic molecules lack repulsive electrostatic interactions, they are more generally expected to show cooperative self-association at low concentration. Indeed, *N*-cyclohexyl-2-pyrrolidinone **6** has been shown to have a rate-retarding effect very similar to that observed for **2d** and **2e**.[7]

The absence of a clear CHIC for the studied hydrotropes is remarkable and in sharp contrast with solubilization experiments.[8] One of the reasons for not observing a clear CHIC may be that the concentration of hydrolytic probe is kept some 3 orders of a magnitude lower than the concentrations of dyes and drugs in typical solubilization experiments.[35] Introducing relatively high concentrations of hydrophobic materials may well induce clustering of the hydrotrope monomers, even when clustering is not occurring in the absence of hydrophobic solubilizates. Similarly, Ueda[22] found that solubilization at low concentrations of solubilizate occurs by one to one complexation, whereas at the higher solubility limits, one to one complexation was no longer sufficient to account for the increased solubilities of apolar compounds. Significantly, da Silva et al.[36] have shown that non-linear increases in solubilizing power and other properties of hydrotrope solutions are not necessarily suggestive of any critical phenomenon.

Conclusion

In the present study, we have examined the effect of a series of charged hydrotropes on the water-catalyzed hydrolysis of **1**. We find that typical hydrotropes stabilize the apolar substrates in aqueous solution by forming encounter complexes with equilibrium constants in the range between 1 kg mol^{-1} and 3 kg mol^{-1}. These equilibrium constants for encounter complex formation are in most cases larger than the equilibrium constants for self-association between hydrotrope monomers as a result of charge repulsion between the latter. The balancing of favorable hydrophobic interaction and unfavorable charge repulsion results in the hydrotropes being soluble over a large concentration range. The mode of action of a hydrotrope differs from the mode of action of a salting-in compound since a hydrotrope contains a hydrophobic moiety, albeit small, that is able to participate in relatively strong hydrophobic interaction with an uncharged apolar molecule. As soon as the hydrophobic moieties are large enough for the hydrophobic interaction to overcome the charge repulsion, cooperative self-association takes place, presumably producing highly dynamic and loose micellar-type aggregates.

Experimental Section

Kinetics

Aqueous solutions were prepared by weight immediately before use. Water was distilled twice in an all-quartz distillation unit. Reactions were monitored at 25.0 ± 0.1°C using appropriate wavelengths to avoid overlap with strong absorption bands of the cosolutes used. Reactions were followed for at least six half-lives using a Perkin-Elmer lambda 2, lambda 5, or lambda 12 spectrophotometer. Good to excellent pseudo-first-order kinetics were obtained, the error in the rate constants being 2% or less. Between 4 and 7 μL of a stock solution containing 1-benzoyl-3-phenyl-1,2,4-triazole **1** in acetonitrile were injected into about 2.7 mL of reaction medium in a 1.000 cm path length stoppered quartz cuvet. The resulting concentrations of hydrolytic probe were about 10^{-5} mol dm^{-3} or less. The pH of every solution was determined using a SENTRON ISFET pH probe and was adjusted to 3.9 ± 0.3 using aqueous HCl. The pH was checked again at the end of each kinetic run and was found to be still well within the pH range in which solely water-catalyzed hydrolysis takes place.

Materials

1-Benzoyl-3-phenyl-1,2,4-triazole,[37,12] sodium 4-*n*-butylbenzenesulfonate[38] and sodium 4-methoxybenzenesulfonate[39] were prepared according to literature procedures. *p*-Toluenesulfonic acid monohydrate, 4-ethylbenzenesulfonic acid, phenyltrimethylammonium bromide and benzyltrimethylammonium bromide were obtained from Aldrich, benzamidinium

chloride was from Sigma, cesium hydroxide hydrate was from Acros and 4-*n*-propylbenzenesulfonyl chloride was from Lancaster and all were used as received. Sodium 4-methylbenzenesulfonate and sodium 4-ethylbenzenesulfonate were prepared by neutralizing the corresponding acid using a sodium hydroxide solution, followed by filtration and evaporation of the solvent. Cesium 4-methylbenzenesulfonate was prepared analogously using CsOH hydrate. All prepared salts were tested and found pure using ^{1}H NMR and elemental analysis. All hydrotropes were stored in a desiccator over P_2O_5 or KOH. NMR spectra were recorded on Varian Gemini 200 (^{1}H: 200 MHz) and VRX 300 (^{1}H: 300 MHz) spectrometers, with HOD set to 4.79 ppm. In the determination of the concentration dependence of the ^{1}H NMR spectra of **2b**, **2d** and **2e**, methanol was added as a second reference. The signal of methanol did not shift with respect to the set signal of HOD. Elemental analyses were performed by H. Draayer and J. Ebels of the analytical section of this department.

Sodium 4-*n*-Propylbenzenesulfonate (2d)

4-*n*-Propylbenzenesulfonyl chloride, 15 g (65 mmol) was suspended in 1 M aqueous NaOH and stirred vigorously for 2 days at 40 °C. The resulting acidic solution was neutralized and the solvent evaporated, resulting in a 1:1 sodium 4-*n*-propylbenzenesulfonate/NaCl mixture; yield: 18.2 g (65 mmol). The mixture was extracted continuously overnight in a Soxhlet apparatus using *n*-propanol. Only part of the sodium 4-*n*-propylbenzenesulfonate was extracted to avoid contamination with NaCl. The absence of sodium chloride was confirmed using a silver nitrate precipitation test. ^{1}H NMR (D_2O): $\delta =$ 0.88 (3H, $CH_2CH_2CH_3$, t), 1.61 (2H, $CH_3CH_2CH_2$, sextet), 2.64 (2H, $CH_3CH_2CH_2$, t), 7.36 and 7.71 (4H, phenyl, AB-system); anal. calcd. for $C_9H_{11}SO_3Na$: C 48.64, H 4.99, S 14.43%; found: C 48.30, H 4.84, S 14.30%.

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